IN THE SPECIFICATION:

Please amend the first paragraph appearing on page 1 (as inserted by the Preliminary Amendment) with a section title as follows:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of application serial number 09/258,882 filed on March 1, 1999, now U.S. Patent 6,589,994, issued July 8, 2003, which is a continuation-in-part application of PCT application PCT/US97/15272 filed on August 29, 1997, which ~~a~~ is a continuation of provisional application serial number 60/025,050 filed on August 30, 1996.

Please delete the first paragraph originally appearing on page 1 in the "as-filed" application immediately after the section title "BACKGROUND OF THE INVENTION" as follows:

~~This application is a continuation-in-part of PCT application PCT/US97/15272, filed August 29, 1997, which was a continuation of application Serial No. 60/025,050, filed August 30, 1996.~~

Please amend the paragraph bridging pages 1 and 2 as follows:

Many agents currently employed in the treatment of ~~pathologies~~ pathologies, such as spasticity and ~~convulsions~~ convulsions, display troubling side-effect profiles ~~which~~ that limit their long-term clinical utility. Among these agents, for example, are the benzodiazepines, which can cause impairment of cognition (impairment of memory-related performance, or "cognitive blunting"). See, for example, ANTIEPILEPTIC DRUGS, Fourth ~~Edition,~~ Edition (Levy ~~*et al.*~~ *et al.*, eds.), Raven ~~Press,~~ Press (1995). Two other clinically used agents are valproate and related therapeutically useful salts such as valproic acid hemisodium salt, which are hepatotoxic and teratogenic, and baclofen, which produces excessive muscle weakness and sedation. These ~~side effects~~ side effects severely limit the therapeutic potential for both drugs. It is apparent, ~~therefore~~ therefore, that improved and better-tolerated treatments for spasticity, convulsions, and other therapeutic indications are greatly ~~to be~~ desired.

Please amend the second full paragraph appearing on page 4 as follows:

~~Figures~~ FIGs. 1a and 1b ~~depicts~~ depict the structures of compounds, including isovaleramide, capable of inducing a modulation of the central nervous system.

Please amend the third full paragraph appearing on page 4 as follows:

~~Figure~~ FIG. 2 portrays the effect of isovaleramide (at 300 mg/kg, i.p.) on gross observational spasticity scores elicited by a metal probe applied to the abdomen in the chronic spinalized rat. Each rat served as its own control; there were three rats per group. The bar at time zero represents pre-treatment control values.

Please amend the fourth full paragraph appearing on page 4 as follows:

~~Figure~~ FIG. 3 illustrates a time-dependent reduction of the flexor reflex, an electrophysiological measure of spasticity, in the chronic spinalized rat. The effects of isovaleramide (300 mg/kg p.o.), baclofen (10 mg/kg s.c.), and vehicle (water, 12 ml/kg p.o.) are shown at pre-treatment (time zero) and at 30, 60, 90, and 120 minutes post-administration. Isovaleramide caused a significant decrease in the magnitude of the flexor reflex, comparable to that observed with baclofen.

Please amend the fifth full paragraph appearing on page 4 as follows:

~~Figure~~ FIG. 4 shows a dose-response relationship for isovaleramide and baclofen, a known antispasticity agent. Isovaleramide and baclofen produced a similar ~~dose-dependent~~ dose-dependent reduction of the flexor reflex in the chronic spinalized rat. The responses from ~~Figure~~ FIG. 3 and response from additional doses were converted to a ~~total-area-under-the-curve~~ total-area-under-the-curve for the two-hour measurement. All drug-related groups were significantly different from the vehicle ($p < 0.05$, ANOVA).

Please amend the paragraph bridging pages 4 and 5 as follows:

~~Figure~~ FIG. 5 shows that isovaleramide was effective in ~~reducing~~ reducing, in a dose-dependent ~~manner~~ manner, the generalized seizure responses of fully kindled rats. Isovaleramide decreased the mean seizure score and the afterdischarge duration in amygdala-kindled rats, showing that it exerts anticonvulsant activity against both focal and secondarily generalized seizures.

Please amend the first full paragraph appearing on page 5 as follows:

~~Figure~~ FIG. 6 illustrates the antiepileptogenesis effect of a daily 500 mg/kg p.o. dose of isovaleramide compared to controls. Isovaleramide elicited a delay in the rate of increase in both seizure score and afterdischarge duration (not shown) which normally develop during electrical kindling in the ~~amygdala-kindled~~ amygdala-kindled rat.

Please amend the paragraph bridging pages 5 and 6 as follows:

A number of pathologies, exemplified by affective mood disorders ~~(i.e.~~ (i.e., bipolar disorder), headaches (chronic, cluster, migraine), restlessness syndromes, neuropathic pain, movement disorders, spasticity, convulsions, cerebral insult, neurodegeneration, and substance abuse have at least one symptom that is usefully alleviated by effecting a modulation of CNS activity. Accordingly, an individual who suffers from such a pathology may be treated with a therapy where, pursuant to the present invention, that individual receives a pharmaceutical formulation of isovaleramide, isovaleric acid, or a related compound.

Please amend the first full paragraph appearing on page 6 as follows:

Without wishing to be bound by any theory, the inventors believe that the compounds of the present invention act via a GABAergic mechanism and, hence, bear a pharmacological similarity to known drugs that are considered to enhance central GABAergic neurotransmission. Like many of the extant drugs, such as the barbiturates, the benzodiazepines, gabapentin, valproic acid and therapeutically useful valproate ~~salts~~ salts, such as valproate hemisodium salt (herein included with reference to valproate), vigabatrin, and progabide, the compounds of the

present invention are effective in treating pathological conditions, illustrated by those mentioned above, that are thought to arise from a defect in the regulation of inhibitory (GABA- and/or glycine-related) neurotransmission.

Please amend the paragraph bridging pages 13 and 14 as follows:

Recent studies have shown that compounds such as GABAergic agents (chlormethiazole, valproate or muscimol) that enhance inhibitory neurotransmission, also can elicit a neuroprotective effect following the same type of cerebral insults described above (Lyden, Chapter 10 in "Neuroprotective Agents and Cerebral ~~Ischaemia",~~ Ischaemia," IRN 40, Academic Press Limited, 1997). GABA and glycine are the primary inhibitory neurotransmitters in the mammalian central nervous system and, therefore, it is expected that enhancement of inhibitory neurotransmission via GABA or glycine ~~agonists~~ agonists, as well as via other agents that have been shown to increase GABA or glycine inhibitory neurotransmission (GABA/glycine reuptake inhibitors, GABA/glycine metabolic inhibitors, GABA/glycine synthesis enhancers, GABA/glycine receptor modulators, ~~etc.)~~ etc.), also will produce a neuroprotective effect. Studies have shown that the combination of the GABA agonist muscimol and the glutamate ~~antagonist,~~ antagonist MK-801 appeared to confer an added neuroprotective effect over either agent alone, although the effect was modest (Lyden, 1997).

Please amend the first full paragraph appearing on page 14 as follows:

Kindling has been proposed as a model to search for drugs with antiepileptogenic efficacy (Wada, *Epilepsia* 19:~~217-227,~~ 217-227 (1974); Sato et al., *Epilepsy Research* 5:~~117-124, (1990));~~ 117-124 (1990); Silver et al., *Ann. Neurol.* 29:~~356-363,~~ 356-363 (1991)). The term "antiepileptogenic" refers to the idea of inhibiting the processes that ~~underly~~ underlie the development of epilepsy. ~~"Anticonvulsant",~~ "Anticonvulsant," on the other hand, refers to the actual inhibition of seizures in an epileptic model.

Please amend the second full paragraph appearing on page 15 as follows:

SUBSTANCE ABUSE/CRAVING: Anticonvulsants such as ~~cambamazepine,~~ carbamazepine, that have shown efficacy in kindled models of epilepsy, have also demonstrated efficacy in reducing the symptoms of affective mood disorders and substance abuse/craving in patients (Post, et al., *Ann. N.Y. Acad. Sci.* ~~537:292-308, (1988));~~ 537: 292-308 (1988); Post, et al., *Epilepsia* 25: ~~234-239, (1984));~~ 234-239 (1984); Post, et al., *Psychopharmacology* 72: ~~189-196, (1981))~~ 189-196 (1981); Halikas et ~~al., 1989;~~ al. (1989); Blumer et ~~al., 1988).~~ al. (1988)). Post and Kopanda (1976) have demonstrated a pharmacologic (chemical) kindling model employing subconvulsive doses of cocaine as the stimulus. The progressive human response to high cocaine usage such as irritability, restlessness, hypervigilance, and paranoia may be a human equivalent of the kindling phenomenon observed in animals.

Please amend the third full paragraph appearing on page 15 as follows:

Several kindling models of seizure development have been characterized. Seizure kindling models are characterized by administration of a sub-seizure eliciting electrical or chemical stimulus (*i.e.*, sub-threshold) over a period of time (Goddard et ~~al.;~~ al., 1969). The majority of initially non-convulsive animals that are exposed to such stimuli over a number of days eventually exhibit seizure activity to these stimuli, have a permanently lowered threshold, exhibit altered manifestations of normal behavior ~~and therefore~~ and, therefore, are considered "kindled." A kindling phenomenon has been proposed to underlie the development of disorders such as certain types of epilepsy syndromes, substance abuse/craving and affective mood disorders such as bipolar (Post et al. 1981, 1984, 1988, ~~supra:~~ supra; Ballenger, et al., *Br. J. Psychiatry* 133: ~~1-14, (1978));~~ 1-14 (1978)).

Please amend the paragraph bridging pages 16 and 17 as follows:

The major, water-soluble, active principle of commonly used valerian extracts and other preparations, such as aqueous or hydroalcoholic extracts or tinctures, has been determined to be the ester hydrolysis product, isovaleric acid. Ammonium isovalerate and isovaleramide are produced in ammoniated tinctures. Balandrin et al., *J. Toxicol.-Toxin Rev.* 14: 165 (1995). The

structures of isovaleramide and related compounds are depicted in ~~Figure 1.~~ FIGs. 1a and 1b. In this way, the chemically labile valepotriates and other valerian-derived monoterpenoid-isovalerate esters, such as bornyl, lavandulyl, and ethyl isovalerates, might be considered to act as "pro-drugs" and chemical precursors for isovaleric acid, its salts, and isovaleramide.

Please amend the first full paragraph appearing on page 17 as follows:

Isovaleramide has been isolated from valerian plants, most probably as an isolation artifact following treatment with ammonia. Buckova *et al.*, ~~*Cesk. Farm.*~~ *Psychopharm.* 26: 308 (1977); *Chem. Abstr.* 88: 86063z (1978); see also Bos *et al.* and Fuzzati *et al.*, *Phytochem. Anal.* 7: 143, 76 (1996). More recently, isovaleramide was shown to exhibit low acute toxicity *in vivo*, no mutagenic potential, and clinically useful anxiolytic properties (U.S. patent No. 5,506,268; PCT application WO 94/28,888). Methods for preparing isovaleramide are well known.

Please amend the paragraph bridging pages 20 and 21 as follows:

Generally, esters of isovaleric acid are expected to be hydrolyzed *in vivo* by ubiquitous esterase enzymes, thereby releasing isovaleric acid and the constituent alcohol. Particularly preferred among the isovalerate esters are glyceryl mono-, di-, and especially tri-isovalerates ("triisovalerin"), isovaleryl salicylic acid or salicylate (salicylic acid isovalerate), ethyl isovalerate, and β-sitosteryl isovalerate. See ~~Figure 1.~~ FIGs. 1a and 1b. Hydrolysis of these isovalerate esters *in vivo* releases isovaleric acid and glycerol (glycerin), salicylic acid (an analgesic, and-inflammatory, and febrifuge), ethanol (ethyl alcohol or common "alcohol," a CNS depressant), and β-sitosterol (a harmless phytosterol), respectively. With the exception of ethyl isovalerate, these esters are non-volatile or only slightly volatile, thereby minimizing any unpleasant odors. Furthermore, in pure ~~form~~ form, these esters possess the advantage of having neutral to pleasant odors, in contrast to the extremely unpleasant odors of isovaleric acid and its salts, such as the ammonium, sodium, potassium, and zinc isovalerate salts. Moreover, whereas ethyl isovalerate is a liquid, the glycerylmono-, di-, and tri-isovalerates, isovaleryl salicylate, and β-sitosteryl isovalerate are expected to be solids at room temperature, thereby facilitating their

formulation into various standard solid and liquid oral dosage forms well known in the art, such as tablets (*e.g.*, uncoated tablets, enteric-coated tablets, and film-coated tablets), capsules, gelcaps, powders, concentrates (drops), elixirs, tinctures, and syrups.

Please amend the first full paragraph appearing on page 21 as follows:

In addition to isovaleramide, various N-substituted amides of isovaleric acid may be used in the inventive methods. These amides can be prepared by methods well known in the art ~~and may~~. See, for example, March, ADVANCED ORGANIC CHEMISTRY: REACTIONS, MECHANISMS, AND STRUCTURE, 4th ed. (John Wiley and Sons 1992). Preferred amides include *N*-ethyl isovaleramide, *N*-methyl isovaleramide, *N,N*-dimethyl isovaleramide, *N*-methyl,*N*-ethyl isovaleramide, N-(2-acetamido)isovaleramide ("*N*-isovaleryl glycinamide"), and *N*-isovaleryl GABA. See, for example, Tanaka *et al.*, *J. Biol. Chem.* 242: 2966 (1967).

Please amend the paragraph bridging pages 21 and 22 as follows:

The structures of these compounds are shown in ~~Figures~~ FIGs. 1a and 1b and include substituted isovaleramides such as 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, and 2,2-dimethyl-n-butyramide. For each of these compounds that contains one or more asymmetric centers, the present invention specifically includes each of the possible enantiomeric or diastereomeric forms of the compound.

Please amend the first full paragraph appearing on page 22 as follows:

N,N-Diethyl isovaleramide ("Valyl"), although purported to possess CNS depressant (sedative) activity, recently has been shown to possess CNS stimulant (convulsant) properties; see U.S. patent No. 5,506,268 and PCT application WO 94/28,888, *supra*. An amide of isovaleric acid with *p*-aminophenol also can be prepared using standard methods to provide a compound, "isovaleraminophen," which is related structurally to the drug acetaminophen

(Tylenol®; see ~~Figure 1).~~ FIG. 1a). In a manner analogous to that of the isovalerate esters, these substituted amides should be hydrolyzed *in vivo* (in this case, via hepatic amidase enzymes), releasing isovaleramide or isovaleric acid.

Please amend the first full paragraph appearing on page 23 as follows:

The compounds of the present invention may be prepared using synthetic methods that are well known in the art. For example, many of the carboxylic acid precursors of the amide compounds are commercially available, for ~~example~~ example, from the Aldrich Chemical Co., Milwaukee, WI, and can be converted into the corresponding amide by preparation of the acid chloride with thionyl chloride or oxalyl chloride, followed by reaction with ammonia or an amine. For compounds containing a hydroxyl group distal to the carboxyl group, the hydroxyl group first is protected using a suitable protecting group as described, for example, in Green, "Protective Groups in Organic ~~Synthesis",~~ Synthesis," Wiley (1981), prior to preparation of the acid chloride. 2-hydroxy and 3-hydroxy isovaleramide are metabolites of isovaleramide *in vivo*, and can be isolated in high yield from the urine of a patient being treated with isovaleramide.

Please amend the second full paragraph appearing on page 24 as follows:

The present invention also is directed to pharmaceutical compositions containing the active compounds described above. The pharmaceutical compositions can contain a single active compound, or can contain combinations of two or more of the active compounds. The pharmaceutical formulations of the present invention can be prepared according to known methods to prepare pharmaceutically useful compositions, whereby active agents are combined in a mixture with a pharmaceutically acceptable carrier. For instance, see REMINGTON'S PHARMACEUTICAL SCIENCES and GOODMAN AND GILMAN'S, both cited above. A composition is said to be in a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers ~~(e.g.~~ (e.g., saline and Ringer's solutions) are well known to those skilled in the art. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*.

Please amend the first full paragraph appearing on page 28 as follows:

There are several models of spasticity including the acute decerebrate rat, the acute or chronic spinally transected rat, and the chronically spinal cord-lesioned rat. (Wright, J., et al., ~~Clin Orthop~~ *Clin. Orthop.* 253:12,~~1990).~~ 1990.) The acute models, although of proven value in elucidating the mechanisms involved in the development of spasticity, have come under criticism due to the fact that they are acute. The animals usually die or have total recovery from spasticity. The spasticity develops immediately upon intervention, unlike the spasticity that evolves in the human condition of spasticity, which most often initially manifests itself as a flaccid paralysis. Only after weeks and months does spasticity develop in humans. Some of the more chronic-lesioned or spinally transected models of spasticity do post-operatively show flaccid paralysis. At approximately four weeks post-lesion/transection, the flaccidity changes to spasticity of variable severity. Although all of these models have their own particular disadvantages and lack of true representation of the human spastic condition, they have provided much information about the nature of spasticity. These models have also provided methods to test various treatment paradigms that have led to similar treatments being tested in humans. Many of these models have also made use of different species, such as cats, dogs, and primates. Baclofen, diazepam, and tizanidine, effective antispastic agents in humans, are effective on different parameters of electrophysiologic assessment of muscle tone in these models.

Please amend the first full paragraph appearing on page 29 as follows:

This is a test of neurological deficits using the method described by Dunham *et al.*, J. Am. Pharm. Assoc. 46: 208-09 (1957). Rats or mice are placed on a rod rotating at a speed of eight turns per minute. The number of animals which drop off the rod before three minutes is counted and the drop-off times are recorded (maximum: 180~~-sec).~~ seconds). Ten rats are studied per group and the test is performed blind. The test compound is administered i.p. 60~~-min~~ minutes prior to testing. Diazepam, a benzodiazepine, is administered at 8 mg/kg, i.p., as the reference substance. A control group administered the vehicle is also included in the study.

Please amend the third full paragraph appearing on page 30 as follows:

Anticonvulsants, such as ~~cambamazepine,~~ carbamazepine, that have shown efficacy in kindled models of epilepsy, have also demonstrated efficacy in reducing the symptoms of affective mood disorders and substance abuse/craving in patients (Post, *J. Clin. Psychiatry* 50: ~~45-47, (1989),~~ 45-47 (1989); Halikas, et al., *Lancet* 18:~~623-624,~~ 623-624 (1989); Blumer et al., *Compr. Psychiatry* 29:~~108-122,~~ 108-122 (1988)).

Please amend the first full paragraph appearing on page 32 as follows:

Acute cerebral ~~insults~~ insults, such as status epilepticus, traumatic injury and ~~stroke~~ stroke, induce damage to selective neuronal populations in the hippocampus (Matsuyama, et al., *J. Cereb. Blood Flow Metab.* 13:~~229-234, (1993));~~ 229-234 (1993); Sloviter, *Science* 235: ~~73-76, (1987))~~ 73-76 (1987)), suggesting that substances designed to prevent the neuronal damage that occurs in a variety of human neurological diseases would be therapeutically useful. Jolkkonen, et al., *Neuroreport* 7:~~2031-2035, (1996)~~ 2031-2035 (1996), found that augmentation of GABAergic inhibition by chronic infusion of the GABA transaminase inhibitor, vigabatrin, prevented the delayed seizure-induced damage following kainate-induced status epilepticus.

Please amend the second full paragraph appearing on page 32 as follows:

Stroke in humans is a highly variable clinical condition, dependent upon pre-existing disease in a patient, the site and severity of the stroke, the type of stroke (ischemic or hemorrhagic), and the time from onset to presentation for treatment. A number of animal models of stroke have been developed over the past several years to aid in our understanding of the pathophysiological mechanisms of neuronal injury and to allow for the evaluation of potential neuroprotective agents (Ginsberg *et al.*, *Stroke* 20: 1627-1642, 1989; Hunter *et ~~al,~~ al.*, *Trends. Pharmacol. Sci.* 16: 123-128, 1996). A major goal of these animal models has been to reduce the biological variability, by controlling or eliminating the variables mentioned above, to facilitate data analysis and interpretation. In doing so, however, these animal models do not perfectly mimic the human condition.

Please amend the paragraph bridging pages 32 and 33 as follows:

Kindling phenomenon has been proposed to underlie the development of ~~disorders~~ disorders, such as epilepsy substance abuse/craving and affective mood disorders such as bipolar (Post et ~~al. 1981:~~ al., 1981; Post et al., 1984; Ballenger et al., 1978; Post et al., 1988). Anticonvulsants, such as ~~cambamazepine,~~ carbamazepine, that have shown efficacy in kindled models of epilepsy, have also demonstrated efficacy in reducing the symptoms of affective mood disorders and substance abuse/craving in patients (Post and Weiss, ~~1989,~~ 1989; Halikas et al., 1989; Blumer et al., 1988). Post et ~~al.,~~ al. (*Biol. Psychiatry* 11: ~~403-419, (1976))~~ 403-419 (1976)), have demonstrated a pharmacologic (chemical) kindling model employing subconvulsive doses of cocaine as the stimulus. The progressive human response to high cocaine ~~usage~~ usage, such as irritability, restlessness, hypervigilance, and ~~paranoia~~ paranoia, may be a human equivalent of the kindling phenomenon observed in animals. Recently, the anticonvulsant drug, vigabatrin, was proposed as a possible treatment for cocaine or nicotine craving (Dewey, et al., *Synapse* ~~31:76,~~ 31: 76 (1999)).

Please amend the first full paragraph appearing on page 36 as follows:

As shown in ~~Figure~~ FIG. 2, isovaleramide at a dose of 300 mg/kg, i.p., was efficacious at 15, 30, 60, and 120 minutes post-administration in reducing the spasticity scores (45-65%). By the next day, *i.e.*, by 1440 minutes (24 hours), the spasticity scores had essentially returned to baseline values. No overt behavioral toxicity or motor impairment was observed at this dose. The rats were alert and able to grasp with their non-paralyzed front paws as were the control, untreated rats.

Please amend the second full paragraph appearing on page 36 as follows:

With reference to ~~Figure~~ FIG. 3, the polysynaptic ~~flexor reflex~~ flexor-reflex responses, to test stimuli which activate high-threshold afferents, were recorded as EMG activity from the ipsilateral hamstring muscle. Supramaximal electric shocks were applied to the hindpaw, and recording electrodes were placed in the biceps femoris semitendinosus muscle. Five sets of stimuli were made at each time point. The flexor reflex was recorded, in both the pre-drug and

the post-drug periods, every 30 minutes once a stable baseline response was achieved. See Hao *et al.*, *Eur. J. Pharmacol.* 191: 407 (1990).

Please amend the third full paragraph appearing on page 36 as follows:

Thus, the responses were determined in spinalized rats by observing the flexor-reflex response ~~(Figure~~ (FIG. 3) before treatment and at each of 30, 60, 90, and 120 minutes following administration of isovaleramide (300 mg/kg p.o.), baclofen (10 mg/kg s.c.) and vehicle (water, 12 ml/kg p.o.), respectively.

Please amend the paragraph bridging pages 36 and 37 as follows:

In ~~Figure~~ FIG. 4, the responses from ~~Figure~~ FIG. 3 and additional doses of isovaleramide and baclofen are converted to a total-area-under-the-curve format, covering the entire, two-hour measurement period. All drug-treated groups differed significantly from the vehicle ($p < 0.05$), based on a one-way analysis of variance. Between the drug-treated groups, no differences were found in total reduction of the flexor reflex over the two-hour period (pairwise multiple comparison, Student-Newman-Keuls method).

Please amend the paragraph bridging pages 43 and 44 as follows:

Adult, male Sprague-Dawley rats weighing at least 230 gr were implanted with a teflon-coated bipolar electrode sterotaxically placed in the anterior basolateral nucleus of the amygdala under ketamine and xylazine anesthesia. The electrode was implanted at the following coordinates with Bregma as zero: AP-2.2 mm, ML-4.7 mm, DV-8.7 mm. After a one-week recovery period, animals were kindled to Stage 5 behavioral seizures using a stimulus consisting of a 50 Hz, 1 sec train of 1 ms biphasic 150 uA pulses that were delivered once daily until 10 consecutive stage 5 seizures were evoked. Testing of isovaleramide was initiated after a one-week, stimulus-free period. On the compound test day, rats displaying a stage 5 seizure were divided into multiple treatment groups ~~(i.e.~~ (i.e., vehicle control and isovaleramide treatment). Sixty minutes after oral dosing, individual rats received a 300 uA, 1 sec duration stimulation and their seizure score and afterdischarge duration recorded. Seizure score was classified according

to Racine (*Electroencephalogr. Clin. Neurophysiol.* ~~32:281-294, (1972): stage~~ 32: 281-294 (1972). Stage 0: no abnormal behavior; stage 1: mouth or facial movements; stage 2: mouth or facial movements and head nodding; stage 3: stage 2 and forelimb clonus; stage 4: stage 3 and rearing; stage 5: stage 4 and falling. A score of 2-3 represents a focal seizure while a score of 4-5 represents secondarily generalized seizures. Afterdischarge duration was the total duration of the amygdala electroencephalogram spikes with an amplitude of at least twice the amplitude of the prestimulus recording and a frequency greater than 1/sec.

Please amend the first full paragraph appearing on page 44 as follows:

Isovaleramide was effective in reducing in a dose-dependent manner the generalized seizure responses of fully kindled rats. Isovaleramide decreased the mean seizure score and the afterdischarge duration showing that it exerts anticonvulsant activity against both ~~focal(seizure~~ focal (seizure score 1-3) and secondarily generalized seizures (seizure score 4-5).

Please amend the paragraph bridging pages 44 and 45 as follows:

In these studies, groups of adult, male Sprague-Dawley rats weighing at least 230 gr were implanted with a teflon-coated bipolar electrode sterotaxically placed in the anterior basolateral nucleus of the amygdala under ketamine and xylazine anesthesia. The electrode was implanted at the following coordinates with Bregma as zero: AP-2.2 mm, ML-4.7 mm, DV-8.7 mm. Chronic treatment with vehicle (0.5% carboxymethylcellulose, p.o.) or isovaleramide (500 mg/kg, p.o., 0.08 ml/gr of body weight) was initiated after a seven-day postoperative recovery period. After a ~~30 min~~ 30-minute pretreatment period, animals were stimulated at a suprathreshold current of 300 uA for 1 second daily (i.e, except weekends) until all control animals exhibited 7 consecutive stage 5 seizures (Racine, 1972). After 11 treatment days, all animals were permitted a 7-day drug- and stimulus-free period. Animals were then challenged with 300 uA once daily starting at day 18 until all animals displayed 5 consecutive stage 5 seizures. Seizure score and afterdischarge duration were recorded after each stimulation. Seizure score was classified according to Racine ~~scale(1972):~~ scale (1972): stage 0, no abnormal behavior; stage 1, mouth or facial movements; stage 2, mouth or facial movements and head nodding; stage 3, stage 2 and

forelimb clonus; stage 4, stage 3 and rearing; stage 5, stage 4 and falling. A score of 2-3 represents a focal seizure while a score of 4-5 represents secondarily generalized seizures. Afterdischarge duration was the total duration of the amygdala electroencephalogram spikes with an amplitude of at least twice the amplitude of the prestimulus recording and a frequency greater than 1/sec. The results demonstrate the ~~antiepiletogenic~~ antiepileptogenic effect of a daily 500 mg/kg p.o. dose of isovaleramide, which delayed the increases in both seizure score and afterdischarge duration which normally develop during electrical kindling in the amygdala-kindled rat. Although isovaleramide at this dose elicited a delay in the acquisition of seizure development, over time, the rats eventually developed full stage 5 seizures. We have shown in the Frings mouse that isovaleramide has a quick onset of action with a relatively short biological half-life. A greater antiepileptogenic effect may have occurred if the dosing schedule had been maximized for longer exposure.